



# Impact of dehydroepiandrosterone on thyroid autoimmunity and function in men with autoimmune hypothyroidism

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Received: 15 June 2020 / Accepted: 18 November 2020  
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## Abstract

**Background** Testosterone administration was found to have a protective effect on thyroid autoimmunity in men with autoimmune (Hashimoto's) thyroiditis. **Objective** The present study was aimed at assessing whether oral dehydroepiandrosterone affects thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity in men with subclinical hypothyroidism induced by Hashimoto's thyroiditis. **Setting** The study was conducted at Medical University of Silesia, Katowice, Poland. **Method** The study enrolled 32 elderly men with autoimmune hypothyroidism and low dehydroepiandrosterone-sulfate levels. Based on patient preference, the participants either received oral dehydroepiandrosterone (50 mg daily; n = 16) or remained untreated (n = 16). Apart from measuring antibody titers and hormone levels, we calculated baseline and post-treatment values of three structure parameters of thyroid homeostasis. **Main outcome measure** Serum titers of thyroid peroxidase and thyroglobulin antibodies. **Results** At baseline, there were no significant differences in the investigated parameters between both groups of men. All participants completed the study. Oral dehydroepiandrosterone increased dehydroepiandrosterone-sulfate and testosterone levels, as well as had a neutral effect on estradiol levels. The increase in dehydroepiandrosterone-sulfate correlated with treatment-induced changes in serum testosterone. Moreover, dehydroepiandrosterone reduced titers of thyroid peroxidase and thyroglobulin antibodies, decreased serum thyrotropin levels, reduced Jostel's thyrotropin index as well as increased thyroid's secretory capacity. Treatment-induced changes in thyroid antibody titers, thyrotropin levels, Jostel's thyrotropin index and thyroid's secretory capacity correlated with the increase in dehydroepiandrosterone-sulfate and testosterone levels. **Conclusion** The obtained results show that exogenous dehydroepiandrosterone may exert a beneficial effect on thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity in men with autoimmune thyroiditis and subclinical hypothyroidism.

**Keywords** Adrenal androgens · Hypothalamic-pituitary-thyroid axis · Thyroid autoimmunity · Thyroid function tests

## Abbreviations

CI	Confidence interval
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone-sulfate
IU	International unit
SD	Standard deviation
SPINA	Structure parameter inference approach
TgAb	Thyroglobulin antibodies
TPOAb	Thyroid peroxidase antibodies

## Impacts on practice

- Exogenous dehydroepiandrosterone reduces thyroid antibody titers in men with Hashimoto's thyroiditis
- The beneficial effect on thyroid autoimmunity is accompanied by the improvement in thyroid function
- Dehydroepiandrosterone treatment may bring benefits to men with autoimmune hypothyroidism

## Introduction

Autoimmune or Hashimoto's thyroiditis, the commonest cause of hypothyroidism in developed countries and the most prevalent organ-specific autoimmune disease worldwide, is characterized by a strong female preponderance,

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suggesting an important role of sex hormones in its development [1, 2]. In line with this hypothesis, men with high values of the estradiol: testosterone ratio were more prone to the development of Hashimoto's thyroiditis than men with low values of this ratio [3], men with thyroid hypofunction secondary in the majority of cases to autoimmune thyroid disease had low circulating testosterone levels [4], while the age of onset of autoimmune thyroiditis was determined by the (CAG)<sub>n</sub> repeat polymorphism of the androgen receptor [5]. Recently, we have found that testosterone therapy of men with impaired activity of the hypothalamic-pituitary-testicular axis reduced thyroid antibody titers [6], while the opposite effect was exerted by spironolactone, a drug with multidirectional antiandrogenic properties [7]. The impact of exogenous testosterone and spironolactone on thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb), considered the biological hallmark of autoimmune thyroiditis [1, 2], correlated with treatment-induced changes in circulating testosterone levels [6, 7]. Unlike testosterone, much less is known about the impact on thyroid autoimmunity of adrenal precursors of androgens. In animal models of autoimmune disorders, dehydroepiandrosterone (DHEA), the main product of the adrenal zona reticularis and the most abundant circulating steroid presents in the human body, suppressed expression of various proinflammatory cytokines and blunted both Th1 and Th2 immunological responses [8]. Women with elevated levels of TPOAb and TgAb were characterized by lower circulating levels of dehydroepiandrosterone sulfate (DHEA-S) than women seronegative for thyroid antibodies [9, 10]. Exogenous DHEA administered to women with autoimmune thyroiditis coexisting with premature ovarian failure reduced titers of TPOAb [10]. No analogous study has been conducted in men.

### Aim of the study

The current study was aimed at investigating whether oral DHEA affects thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity in men with subclinical autoimmune hypothyroidism.

### Ethics approval

The research protocol was approved by a local institutional review board (the Bioethical Committee of the Medical University of Silesia [KNW/0022/KB/208/17]) and the study was conducted in accordance with the Declaration of Helsinki and its latest revision. All participants gave their written informed consent to take part in the study.

## Methods

### Patients

The participants of the study ( $n = 32$ ) were recruited among elderly men (60–85 years old) with untreated autoimmune hypothyroidism and low DHEA-S levels. To be included, they were required to meet the following criteria: (a) serum thyrotropin levels between 4.5 and 10.0 mU/L coexisting with free thyroxine levels between 10.0 and 21.0 pmol/L and free triiodothyronine levels between 2.3 and 6.5 pmol/L; (b) serum TPOAb titers above 100 U/mL; (c) multiple hypoechoic micronodules or pseudonodules with poorly-defined margins; and (d) serum DHEA-S levels below 2.8  $\mu$ mol/L.

The exclusion criteria were as follows: positive serum antibodies against thyrotropin receptor; other autoimmune or endocrine disorders; prostate-specific antigen levels above 4 ng/mL (or above 3 ng/mL in men at high risk of prostate cancer); hepatic or renal failure; malabsorption syndrome; body mass index above 35 kg/m<sup>2</sup>; unstable coronary artery disease, myocardial infarction or stroke within 6 months preceding the study; diabetes mellitus; symptomatic congestive heart failure; poorly controlled arterial hypertension; nephrotic syndrome; bronchial asthma or chronic obstructive pulmonary disease; chronic pancreatitis; any other chronic inflammatory processes; prostate, testicular or breast cancer or any other malignant neoplasm; serious inherited disorders; risky or binge drinking<sup>1</sup> and poor compliance. Men receiving within 4 months before the beginning of the study levothyroxine or other drugs affecting hypothalamic-pituitary-thyroid axis activity or thyroid autoimmunity<sup>2</sup> were also excluded.

### Study design

All enrolled men were informed by the investigators about the benefits and possible adverse effects of exogenous DHEA. Based on patient preference, the participants either received DHEA (50 mg daily;  $n = 16$ ) or were not treated with this agent ( $n = 16$ ). DHEA was administered orally once daily in the morning for six months. Most (88%) patients in

<sup>1</sup> Risky drinking was defined as alcohol consumption exceeding 14 standard drinks per week or 4 standard drinks per day; binge drinking was defined as five or more standard drinks on a single occasion; while a standard drink was defined as one 12-oz bottle of beer, one 5-oz glass of wine, or 1.5 oz of distilled spirits.

<sup>2</sup> Aminoglutethimide, amiodarone, anabolic steroids, antithyroid agents, bexarotene, cholecalciferol and its analogs, cholestyramine, colestipol, dopamine, estrogens, fluorouracil, furosemide, glucocorticoids, interferon- $\alpha$ , interleukin-2, iodides, lithium, methadone, mitotane, myo-inositol, nonsteroidal anti-inflammatory drugs, octreotide, perchlorates, salicylates, selenium, slow-release nicotinic acid or tamoxifen.

each groups were treated with other medications. DHEA-treated subjects received angiotensin-converting enzyme inhibitors ( $n = 3$  [19%]), sartans ( $n = 4$  [25%]), calcium channel blockers ( $n = 6$  [38%]), thiazides ( $n = 7$  [44%]),  $\beta$ -blockers ( $n = 3$  [19%]), statins ( $n = 8$  [50%]), fibrates ( $n = 1$  [6%]), thienopyridines ( $n = 4$  [25%]), bisphosphonates ( $n = 2$  [13%]), allopurinol ( $n = 1$  [6%]), febuxostat ( $n = 1$  [6%]), proton-pump inhibitors ( $n = 2$  [13%]), tamsulosin ( $n = 5$  [31%]), finasteride ( $n = 3$  [19%]) and zolpidem ( $n = 4$  [25%]); while DHEA-naïve patients received angiotensin-converting enzyme inhibitors ( $n = 2$  [13%]), sartans ( $n = 3$  [19%]), calcium channel blockers ( $n = 7$  [44%]), thiazides ( $n = 8$  [50%]),  $\beta$ -blockers ( $n = 2$  [13%]), statins ( $n = 6$  [38%]), ezetimibe ( $n = 2$  [13%]), thienopyridines ( $n = 3$  [19%]), denosumab ( $n = 2$  [13%]), allopurinol ( $n = 2$  [13%]), proton-pump inhibitors ( $n = 2$  [13%]), tamsulosin ( $n = 6$  [38%]), finasteride ( $n = 2$  [13%]), zolpidem ( $n = 2$  [13%]) and hydroxyzine ( $n = 1$ ; [6%]). Subjects taking other medications kept their pharmacologic schedule constant. Treatment compliance was assessed by tablet counting and interviews with the patients during each visit, taking place every six weeks. Medication adherence was regarded as satisfactory if the number of tablets returned ranged from 0 to 10% and all four questions in the Polish version of the Morisky-Green test were answered with a “no”.

### Laboratory assays

Venous blood samples were obtained from the antecubital vein between 7.00 and 8.00 a.m. after an overnight 12-h fasting in the first and last day of the study. Serum levels of thyrotropin, free thyroxine, free triiodothyronine, DHEA-S, testosterone and estradiol, and serum titers of TPOAb and TGAb were assayed in duplicate by direct chemiluminescence using acridinium ester technology (ADVIA Centaur XP Immunoassay System, Siemens Healthcare Diagnostics, Munich, Germany). Serum concentrations of creatinine were measured with standard methods (Roche Diagnostics, Basel, Switzerland). The structure parameters of thyroid homeostasis were calculated using SPINA-Thyr 4.0.1 for Windows software. Jostel's thyrotropin index was calculated using the formula:  $\ln [\text{thyrotropin}] + 0.1345 \times \text{free thyroxine}$  [11]. The structure parameter inference approach (SPINA)-GT was calculated as follows:  $\beta_T \times (D_T + \text{thyrotropin}) \times (1 + K_{41} \times \text{standard concentration of thyroxine-binding globulin} + K_{42} \times \text{standard concentration of transthyretin} \times \text{free thyroxine}) / (\alpha_T \times \text{thyrotropin})$  [12]. SPINA-GD was calculated according to the following formula:  $\beta_{31} \times (K_{M1} + \text{free thyroxine}) (1 + K_{30} \times \text{standard concentration of thyroxine-binding globulin}) \times \text{free triiodothyronine} / (\alpha_{31} \times \text{free thyroxine})$  [13]. The following constants were used in the equations:  $\beta_T = 1.1 \times 10^{-6}/s$ ,  $D_T = 2.75 \text{ mU/L}$ ,  $K_{41} = 2 \times 10^{10} \text{ L/mol}$ , standard concentration of thyroxine-binding

globulin =  $300 \text{ nmol/L}$ ,  $K_{42} = 2 \times 10^8 \text{ L/mol}$ , standard concentration of transthyretin =  $4.5 \text{ mmol/L}$ ,  $\alpha_T = 0.1/\text{L}$ ,  $\beta_{31} = 8 \times 10^{-6}/s$ ,  $K_{M1} = 5 \times 10^{-7} \text{ mol/L}$ ,  $K_{30} = 2 \times 10^9 \text{ L/mol}$  and  $\alpha_{31} = 0.026/\text{L}$  [12, 13]. The estimated glomerular filtration rate was calculated as follows:  $175 \times [\text{serum creatinine} (\mu\text{mol/L}) \times 0.0113]^{-1.154} \times \text{age (years)}^{0.203}$  (the Modification Diet in Renal Disease Study equation).

### Statistical analysis

First, the Kolmogorov–Smirnov test was used to analyze the normality of the distribution of the parameters measured. As no variable was normally distributed, all investigated parameters were log-transformed to overcome heteroscedastic error. Because logarithmically transformed data met assumptions of normality and equal variance, parametric tests were used for statistical analysis. Between-group comparisons were performed by Student's *t*-tests for independent samples. The differences between the means of variables within the same study group were analyzed with Student's paired *t*-test. Moreover, to verify the correctness of the statistical analysis, the median values of the investigated parameters were recalculated using nonparametric statistics (the Mann–Whitney *U*-test and the Wilcoxon matched paired test), and the same results were obtained. The  $\chi^2$  test was employed to compare qualitative variables. The importance of each result was assessed based on the 95% confidence interval. The Benjamini–Hochberg procedure was employed to correct for multiple comparisons and decrease false discovery rates. Correlations were calculated using Pearson's correlation coefficient (*r*). Differences were considered statistically significant if 95% confidence intervals did not include the null value and/or two-tailed *p* values were below 0.05.

### Results

At baseline, both groups were comparable with respect to age, body mass index, smoking and drinking habits, hormone levels, antibody titers, all calculated parameters of thyroid homeostasis and the estimated glomerular filtration rate (Table 1). Because DHEA treatment was well tolerated, all participants completed the study and were included in the statistical analyses. In untreated patients, serum antibody titers, hormone levels and all structure parameters of thyroid homeostasis remained at the similar levels throughout the study. Expectedly, oral DHEA increased circulating levels of DHEA-S and testosterone. Moreover, DHEA reduced titers of thyroid peroxidase and thyroglobulin antibodies, decreased serum thyrotropin levels, reduced Jostel's thyrotropin index as well as increased SPINA-GT. The drug has a neutral effect on circulating levels of free thyroxine, free

**Table 1** Baseline characteristics of patients

Variable	DHEA-treated men	DHEA-naive men	Difference (95% CI)
Number of patients	16	16	–
Age [years; mean (SD)]	70 (7)	71 (6)	1 (– 4, 6)
Smokers (%)	25	31	–
Abstainers (%)	75	69	–
Weekly alcohol consumption (standard drinks; mean (SD))	5.3 (2.0)	5.5 (2.2)	– 0.2 (– 1.7, 1.3)
Body mass index (kg/m <sup>2</sup> ; mean (SD))	27.5 (4.0)	27.1 (4.4)	– 0.4 (– 3.4, 2.6)
TPOAb (IU/mL; mean (SD))	750 (302)	802 (355)	52 (– 186, 290)
TgAb (IU/mL; mean (SD))	735 (342)	724 (298)	– 11 (– 243, 221)
Thyrotropin (mIU/L; mean (SD))	7.7 (1.3)	7.6 (1.2)	– 0.1 (– 1.0, 0.8)
Free thyroxine (pmol/L; mean (SD))	15.0 (2.1)	15.1 (2.5)	0.1 (– 1.6, 1.8)
Free triiodothyronine (pmol/L; mean (SD))	3.6 (0.7)	3.8 (0.8)	0.2 (– 0.3, 0.7)
Jostel's thyrotropin index (mean (SD))	4.1 (0.1)	4.1 (0.1)	0.0 (– 0.1, 0.1)
SPINA-GT (pmol/s; mean (SD))	1.55 (0.19)	1.56 (0.21)	0.01 (– 0.13, 0.15)
SPINA-GD (nmol/s; mean (SD))	22.19 (3.02)	23.27 (2.81)	1.08 (– 1.03, 3.19)
DHEA-S (μmol/L; mean (SD))	2.1 (0.4)	2.2 (0.4)	0.1 (– 0.2, 0.4)
Testosterone (nmol/L; mean (SD))	7.2 (0.8)	7.0 (0.9)	– 0.2 (– 0.8, 0.4)
Estradiol (pmol/L; mean (SD))	73 (15)	80 (18)	7 (– 5, 19)
Estimated glomerular filtration rate (mL/min/1.73m <sup>2</sup> ; mean (SD))	81 (11)	83 (12)	2 (– 6, 10)

CI: confidence interval; DHEA: dehydroepiandrosterone; DHEA-S: dehydroepiandrosterone-sulfate; IU: international unit; SD: standard deviation; SPINA: structure parameter inference approach; TgAb: thyroglobulin antibodies; TPOAb: thyroid peroxidase antibodies

triiodothyronine and estradiol, as well as on SPINA-GD and the estimated glomerular filtration rate (Table 2). Both study groups differed in post-treatment values of DHEA-S, testosterone, thyroid antibody titers, thyrotropin levels, Jostel's thyrotropin index and SPINA-GT (Table 2).

Baseline antibody titers correlated with baseline thyrotropin levels (TPOAb:  $r=0.61$ ,  $p<0.001$ ; TgAb:  $r=0.52$ ,  $p<0.001$ ) and baseline SPINA-GT (TPOAb:  $r=-0.31$ ,  $p<0.05$ ; TgAb:  $r=-0.25$ ,  $p<0.05$ ). In patients receiving oral DHEA, the increase in DHEA-S correlated with treatment-induced changes in TPOAb titers ( $r=0.49$ ,  $p<0.001$ ), TgAb titers ( $r=0.42$ ,  $p<0.001$ ), thyrotropin levels ( $r=0.39$ ,  $p<0.001$ ), Jostel's thyrotropin index ( $r=0.37$ ,  $p<0.01$ ), SPINA-GT ( $r=0.44$ ,  $p<0.001$ ) and testosterone levels ( $r=0.48$ ,  $p<0.001$ ). Moreover, (a) DHEA-induced changes in thyrotropin levels correlated with the changes in TPOAb titers ( $r=0.52$ ,  $p<0.001$ ), TgAb titers ( $r=0.48$ ,  $p<0.001$ ), Jostel's thyrotropin index ( $r=0.57$ ,  $p<0.001$ ) and SPINA-GT ( $r=0.50$ ,  $p<0.001$ ), (b) treatment-induced changes in Jostel's thyrotropin index correlated with the impact of DHEA on TPOAb titers ( $r=0.46$ ,  $p<0.001$ ), TgAb titers ( $r=0.40$ ,  $p<0.001$ ) and SPINA-GT ( $r=0.38$ ,  $p<0.01$ ); (c) DHEA-induced changes in SPINA-GT correlated with the decrease in TPOAb titers ( $r=0.41$ ,  $p<0.001$ ) and TgAb titers ( $r=0.36$ ,  $p<0.01$ ); (d) treatment-induced changes in TPOAb titers correlated with baseline TPOAb titers ( $r=0.58$ ,  $p<0.001$ ), baseline TgAb titers ( $r=0.47$ ,  $p<0.001$ ) and the reduction in TgAb titers ( $r=0.65$ ,

$p<0.001$ ); as well as (e) treatment-induced changes in TgAb titers correlated with baseline TPOAb ( $r=0.47$ ,  $p<0.001$ ) and TgAb ( $r=0.51$ ,  $p<0.001$ ) titers. There were also correlations between the effect of DHEA on testosterone levels ( $r=0.37$ ,  $p<0.01$ ) and its impact on TPOAb ( $r=0.34$ ,  $p<0.05$ ), TgAb ( $r=0.31$ ,  $p<0.05$ ), thyrotropin levels ( $r=0.28$ ,  $p<0.05$ ), Jostel's thyrotropin index ( $r=0.32$ ,  $p<0.05$ ) and SPINA-GT ( $r=0.30$ ,  $p<0.05$ ). No other correlations were reported.

## Discussion

The present study enrolled elderly men with mild autoimmune thyroid hypofunction. A relative narrow age range helped to obtain two relatively homogenous groups of patients. The prevalence of autoimmune thyroiditis in men is growing worldwide [14]. Hypothyroidism occurs more often in elderly patients [15], and these patients are often treated with levothyroxine. However, levothyroxine interacts with or its absorption is affected by many drugs commonly used by the geriatric population, including anticoagulants, antidiabetics, antidepressants, sympathomimetics, cardiac glycosides,  $\beta$ -blockers, anti-arrhythmics, anti-convulsants, some statins, antacids, proton pump inhibitors, calcium salts, cimetidine and oral iron [16]. Moreover, the risk of levothyroxine intolerance increases with age [17]. Therefore, levothyroxine does not seem to be an ideal drug for elderly

**Table 2** The effect of oral dehydroepiandrosterone on thyroid antibody titers, hormones, thyroid function tests and estimated glomerular filtration rate in elderly men with Hashimoto's thyroiditis

Variable	DHEA-treated men	DHEA-naïve men	Difference (95% CI)
TPOAb (IU/mL; mean (SD))			
Baseline	750 (302)	802 (355)	52 (− 186, 290)
After 6 months	524 (225) <sup>#</sup>	774 (316)	250 (52, 448)*
Change	− 226 (75)	− 28 (− 15)	198 (159, 237) <sup>&amp;</sup>
TgAb (IU/mL; mean (SD))			
Baseline	735 (342)	724 (298)	− 11 (− 243, 221)
After 6 months	498 (240) <sup>#</sup>	701 (301)	203 (6, 400)*
Change	− 237 (104)	− 23 (20)	214 (160, 268) <sup>&amp;</sup>
Thyrotropin (mIU/L; mean (SD))			
Baseline	7.7 (1.3)	7.6 (1.2)	− 0.1 (− 1.0, 0.8)
After 6 months	6.4 (1.8) <sup>#</sup>	7.6 (1.4)	1.2 (0.1, 2.3)*
Change	− 1.3 (0.4)	0.0 (0.3)	− 1.3 (− 1.6, − 1.0) <sup>&amp;</sup>
Free thyroxine (pmol/L; mean (SD))			
Baseline	15.0 (2.1)	15.1 (2.5)	0.1 (− 1.6, 1.8)
After 6 months	15.5 (2.5)	15.2 (2.8)	− 0.3 (− 2.2, 1.6)
Change	0.5 (0.7)	0.1 (0.5)	− 0.4 (− 0.9, 0.1)
Free triiodothyronine (pmol/L; mean (SD))			
Baseline	3.6 (0.7)	3.8 (0.8)	0.2 (− 0.3, 0.7)
After 6 months	3.8 (0.8)	3.9 (0.7)	0.1 (− 0.4, 0.6)
Change	0.2 (0.2)	0.1 (0.2)	− 0.1 (− 0.3, 0.1)
Jostel's thyrotropin index (mean (SD))			
Baseline	4.1 (0.1)	4.1 (0.1)	0.0 (− 0.1, 0.1)
After 6 months	3.9 (0.1) <sup>#</sup>	4.1 (0.1)	0.2 (0.1, 0.3)*
Change	− 0.2 (0.1)	0.0 (0.1)	0.2 (0.1, 0.3) <sup>&amp;</sup>
SPINA-GT (pmol/s; mean (SD))			
Baseline	1.55 (0.19)	1.56 (0.21)	0.01 (− 0.13, 0.15)
After 6 months	1.69 (0.16) <sup>#</sup>	1.57 (0.15)	− 0.12 (− 0.23, − 0.01)*
Change	0.14 (0.03)	0.01 (0.02)	− 0.13 (− 0.15, 0.11) <sup>&amp;</sup>
SPINA-GD (nmol/s; mean (SD))			
Baseline	22.19 (3.02)	23.27 (2.81)	1.08 (− 1.03, 3.19)
After 6 months	22.67 (2.51)	23.72 (2.46)	1.05 (− 0.74, 2.84)
Change	0.48 (0.11)	0.45 (0.14)	− 0.03 (− 0.12, 0.06)
DHEA-S (μmol/L; mean (SD))			
Baseline	2.1 (0.4)	2.2 (0.4)	0.1 (− 0.2, 0.4)
After 6 months	2.9 (1.1) <sup>#</sup>	2.2 (0.5)	− 0.7 (− 1.3, − 0.1)*
Change	0.8 (0.6)	0.0 (0.2)	− 0.8 (− 1.1, − 0.5) <sup>&amp;</sup>
Testosterone (nmol/L; mean (SD))			
Baseline	7.2 (0.8)	7.0 (0.9)	− 0.2 (− 0.8, 0.4)
After 6 months	7.9 (1.1) <sup>#</sup>	7.1 (1.0)	− 0.8 (− 1.5, − 0.1)*
Change	0.7 (0.3)	0.1 (0.2)	− 0.6 (− 0.8, − 0.4) <sup>&amp;</sup>
Estradiol (pmol/L; mean (SD))			
Baseline	73 (15)	80 (18)	7 (− 5, 19)
After 6 months	78 (12)	82 (16)	4 (− 6, 14)
Change	5 (6)	2 (4)	− 3 (− 7, 1)
Estimated glomerular filtration rate (ml/min/1.73m <sup>2</sup> ; mean (SD))			
Baseline	81 (11)	83 (12)	2 (− 6, 10)
After 6 months	84 (13)	85 (12)	1 (− 8, 10)
Change	3 (2)	2 (2)	− 1 (− 3, 1)

CI: confidence interval; DHEA: dehydroepiandrosterone; DHEA-S: dehydroepiandrosterone-sulfate; IU: international unit; SD: standard deviation; SPINA: structure parameter inference approach; TgAb: thyroglobulin antibodies; TPOAb: thyroid peroxidase antibodies

\*Statistically significant difference between both groups

<sup>#</sup>Statistically significant difference between post-treatment and baseline values in the same group

<sup>&</sup>Statistically significant difference between the changes in both groups



patients with mild thyroid hypofunction. Theoretically, DHEA may be an interesting alternative because in men over the age of 40, secretion of adrenal androgens progressively declines, often reaching very low or negligible levels in the elderly [18].

The current study has shown for the first time that oral DHEA decreases titers of TPOAb and TgAb in men with autoimmune thyroiditis. The inhibitory effect on antibody titers was accompanied by a reduction in circulating levels of thyrotropin, by a decrease in Jostel's thyrotropin index, quantitatively assessing the thyrotropic function of the adeno-hypophysis [11], by an increase in SPINA-GT, measuring thyroid's secretory capacity [12, 13], as well as by unaltered SPINA-GD, determining overall peripheral deiodinase activity [12, 13]. These findings seem to be clinically relevant. Subclinical hypothyroidism, observed in our patients, should not be regarded as a mere laboratory abnormality. It represents a well-defined, often symptomatic disease, associated with adverse health outcomes and is characterized by thyroid hormone production that is persistently insufficient to maintain euthyroidism [19, 20]. The elevation of thyrotropin levels above the upper limit of normal reflects the sensitivity of thyrotropic cells to mild thyroid hypofunction, despite that free thyroxine and free triiodothyronine are still within the reference range [19]. The obtained results suggest that DHEA slightly improves functioning of the hypothalamic-pituitary-thyroid axis at the level of the thyroid and the pituitary in this group of patients by reducing lymphocytic infiltration of the thyroid gland and by normalizing thyrotropin response to thyrotropin-releasing hormone, which is supraphysiological in subclinical hypothyroidism [19]. Owing to the exclusion criteria, our findings cannot be explained by interactions of DHEA with levothyroxine or other drugs known to affect the hypothalamic-pituitary-thyroid axis and/or thyroid autoimmunity. In turn, taking into account similar titers of thyroid antibodies, similar levels of all investigated hormones and similar values of the calculated parameters of thyroid homeostasis in DHEA-naïve subjects before and at the end of the study period, and that participants were enrolled throughout the year, the obtained results cannot be regarded as secondary to seasonal fluctuations in the studied parameters, as well as cannot be explained by spontaneous resolution of Hashimoto's thyroiditis in the investigated population of patients. They are not associated with the changes in renal function because the estimated glomerular filtration rate did not correlate with thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity and was not affected by DHEA treatment. Finally, alcohol consumption does not seem explain the obtained results, because most participants were abstainers, the mean alcohol consumption in the remaining ones was small and did not differ between both study groups.

It is difficult to explain molecular mechanisms underlying the beneficial effect of DHEA in the current study.

Endogenous DHEA exerts its action directly by binding to or activating peroxisome proliferators activated receptors, pregnane X receptor and constitutive androstano receptor or by affecting the nuclear factor kappa-light-chain-enhancer of activated B cells signal transduction pathway [21], as well as indirectly through conversion to downstream hormones: androgens and estrogens [8]. The obtained results suggest that the impact on thyroid autoimmunity and hypothalamic-pituitary-thyroid axis activity is, at least partially, mediated by testosterone because DHEA-induced increase in serum levels of testosterone correlated with the increase in DHEA-S. Moreover, treatment-induced changes in serum testosterone and serum DHEA-S were characterized by similar correlations with the impact on the markers of thyroid autoimmunity and thyroid functioning. Assuming the correctness of this hypothesis, testosterone (and maybe also dihydrotestosterone) deriving from DHEA may alleviate thyroid autoimmunity by affecting the androgen receptor in primary lymphoid organs and peripheral immune cells [22]. Unlike androgens, estrogens do not seem to contribute to this effect. Firstly, autoimmune thyroid disorders are characterized by female preponderance and are diagnosed usually between puberty and menopause, when estrogen production is highest [23]. This suggests that estrogens induce or exacerbate but do not alleviate thyroid autoimmunity. Moreover, in the current study DHEA did not affect estrogen levels and there were no correlations between concentrations of circulating estradiol and thyroid antibody titers, hormone levels and the calculated parameters of thyroid homeostasis. More probable is a direct inhibitory effect of DHEA treatment on cytokine production, found by other investigators [24, 25]. In line with this hypothesis, proinflammatory cytokines contribute to the development of autoimmune thyroiditis and the impact on their production seems to be in part responsible for the decrease in thyroid antibody titers in euthyroid women with Hashimoto's thyroiditis receiving levothyroxine, selenomethionine or levothyroxine/selenomethionine combination therapy [26].

We can only speculate about the clinical relevance of our findings. The study population included elderly men with the senescent decline of the adrenal cortex production of endogenous DHEA and the age-related decline in testosterone levels. However, DHEA treatment may bring clinical benefits not only to this group of men with autoimmune hypothyroidism. This treatment may also be effective in subjects without dysfunction of the adrenal zona reticularis and without hypotestosteronemia. This hypothesis, which should be verified in future studies, is supported by the finding that DHEA-induced changes in antibody titers, serum thyrotropin, pituitary thyrotropic function and thyroid's secretory capacity did not correlate with baseline serum concentrations of DHEA-S and testosterone. In turn, the association between the degree of reduction in TPOAb and TgAb and baseline titers of thyroid antibodies suggests that men with advanced

Hashimoto's thyroiditis may be better candidates for DHEA therapy than subjects with early stages of this disorder.

Some study limitations should be acknowledged. The small number of participants, the non-randomized nature of the study and the lack of placebo-treated patients make drawing any strong conclusions difficult. It cannot be ruled out that the obtained results may have been affected by selection bias and confounding factors. Because treatment compliance was assessed by tablet counting and interviews, some participants could have misplaced tablets rather than take them daily. Supervised administration of tablets would have been better to monitor medication adherence. Taking into account that the study population inhabited the area with low selenium [27] and adequate iodine [28] supply, it cannot be excluded that the impact of DHEA may be different in patients with sufficient selenium and/or inadequate iodine intake. It cannot be also ruled out that the effect of DHEA does not have to be the same in patients receiving levothyroxine, selenium, vitamin D or other drugs influencing hypothalamic-pituitary-thyroid axis activity. Finally, because the study included only men with mild subclinical hypothyroidism, the question whether DHEA affects thyroid function in subjects with overt thyroid hypofunction requires further research.

## Conclusion

Six-month treatment of elderly men with autoimmune thyroiditis with oral DHEA led to a decrease in serum titers of TPOAb and TgAb, as well as partially normalized hypothalamic-pituitary-thyroid axis activity. The beneficial effect of exogenous DHEA correlated with baseline titers of thyroid antibodies and with treatment-induced increases in DHEA-S and testosterone. The obtained results indicate that DHEA alleviates thyroid autoimmunity and improves thyroid function in the studied population of men. Owing to study limitations, our findings need to be verified in larger clinical trials.

**Acknowledgements** The authors would like to thank Ewa Zmuda, a professional translator, for English language editing.

**Funding** This work was not supported by any external source of funding.

**Conflicts of interest** The authors declare they have no conflicts of interest.

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